protease inhibitor. Support for these claims is present in the specification at page 6, lines 1 to 13, the originally filed claims and in experimental section, where serine protease inhibitors are demonstrated to be effective in reversing the effects of long term potentiation. With respect to Claims 32 to 34 these claims find similar support in the application, see e.g., page 6, lines 14 to 18 and the originally filed claims. With respect to Claim 35 to 37, these claims find support in the specification at page 8, lines 3 to 11 and the working exemplification showing that serine protease cleavage of extracellular cell adhesion molecules can contribute to such neurological conditions in the brain. With respect to Claims 38 to 42, these claims find support in a manner analogous to that of Claims 26 to 31. The above discussion demonstrates that new claims 26 to 37 introduce no new matter to the application. As the above new claims introduce no new matter to the application, their entry by the Examiner is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

Rejections

35 U.S.C. § 112, 1st ¶

Claims 1 to 25 were been rejected under 35 U.S.C. § 112, 1st ¶ for the asserted reason that these claims were not enabled by the specification as filed. In view of the cancellation of Claims 1 to 25, this rejection is moot.

With respect to the new Claims 26 to 42, it is respectfully submitted that these claims which are directed to treating specific types of disease conditions with a defined class of agents, i.e., serine protease inhibitors, are fully enabled by the specification which provides extensive written description and working exemplification demonstrating that serine protease inhibitors are effective to treat the defined types of conditions specified in these newly presented claims.

As such, this rejection may be withdrawn.

35 U.S.C. § 112, 2nd ¶

Originally filed Claims 1 to 25 were rejected under 35 U.S.C. § 112,2nd ¶ for using a number of different terms which assertedly rendered the claims ambiguous. In view of the cancellation of Claims 1 to 25, this rejection is moot. Furthermore, new Claims 26 to 42 do not employ these terms. As such, the rejection does not apply against the newly presented claims.

35 U.S.C. § 103

Claims 1 to 25 were rejected under 35 U.S.C. § 103 as being unpatentable over Freidrich, Okajima, Veronesi and Pinsky, in view of Kazmirowski. In making this rejection, the Examiner reasoned that the cited primary references teach the general approach of treating neurological conditions with protease inhibitors, and the supplemental Kazmirowski reference discloses the specific aminobenzenesulfonyl compounds employed in the experimental section. As such, the Examiner reasons that what the applicants have done is merely elucidate the mechanism of a method that has been inherently practiced in the prior art, and therefore have not made a patentable invention.

With respect to newly presented Claims 26 to 42, these claims are directed to the treatment/prevention of specific neurological conditions. It is respectfully submitted that, absent the data provided in the present application and working exemplification, one of skill in the art would not have found it obvious to employ serine protease inhibitors for the treatment of the conditions specified in the claims because the cited prior art references provide no suggestion or guidance as to the effectiveness of serine protease inhibitors in the treatment of the specified disease conditions.

For example, Claims 26 to 31 are specifically directed to treating conditions associated with an undesirable increase in synaptic responsiveness, such as is observed in epileptic patients. The Applicants have made these claims following their observed results of the Kindling Assays reported in the experimental section of the present application. The Kindling Assay employed by the Applicants is well accepted by those of skill in the art as a model of human conditions that

result from undesirable synaptic responsiveness, e.g. epilepsy. As such, the Kindling Assay employed by the Applicants is an art accepted model of human epilepsy and related disease conditions associated with synaptic responsiveness. In fact, the Kindling Assay is the only art accepted model of epilepsy, and any other type of assay is not accepted as indicative of what will and will not be effective in treating epilepsy and related disorders. In the work performed by the Applicants, the Applicants showed that serine protease inhibitors were effective in treating symptoms brought about in the Kindling Assays. As such, only after the Applicants showed that serine protease inhibitors are effective in the Kindling Assay would one of skill in the art have a reasonable expectation of success that serine protease inhibitors would exhibit any activity, much less desirable therapeutic activity, in treating conditions characterized by excessive synaptic activity and/or synaptic responsiveness.

Turning now to the cited references, Freidrich provides experimental evidence directed to the use of antithrombin compounds to promote neurite growth. Showing that an agent increases neurite growth teaches nothing about whether it reduces the adverse effects of synaptic over-activation or excessive glutamate receptor activity. As such, one of skill in the art would have no idea based on Freidrich as to whether serine protease inhibitors would have any effect, much less a therapeutic effect, on disease conditions associated with synaptic responsiveness or glutamate receptor activity, as is now claimed. As pointed out above, one of skill in the art can not know whether a particular type of agent will have activity therapeutic activity with respect to conditions characterized by increased synaptic responsiveness and/or increased synaptic activity unless a representative of that particular type of agent is tested in a Kindling assay.

Okajima describes the use of antithrombin III for prevention and treatment of "motor functional disturbance, tissue injury, spinal injury, and spinal ischemia." Since Okajima reports no Kindling Assay data and does not even mention the particular disease conditions that are the subject of the presently pending claims after entry of the above amendment, Okajima also fails to provide any indication that serine protease inhibitors will have any activity, much less a therapeutic activity, with respect to the conditions now claimed.

Veronesi reports using PMSF to protect rats from neurological damage following exposure to Mipafox. As such, this report is based on preventing damage following exposure to a neurotoxin. Since Veronesi is concerned with preventing the effects of a neurotoxin, Veronesi says nothing about the disease conditions that are the subject of the pending claims. Since Veronesi reports no Kindling Assay data and does not even mention the particular disease conditions that are the subject of the presently pending claims after entry of the above amendment, this reference also fails to provide any indication that serine protease inhibitors will have any activity, much less a therapeutic activity, with respect to the conditions now claimed.

Pinsky reports the effect of peptidase inhibitors on rats undergoing narcotic withdrawal. Since Pinsky is concerned with the effects of narcotic withdrawal, Pinsky says nothing about the disease conditions that are the subject of the pending claims. Since Pinsky reports no Kindling Assay data and does not even mention the particular disease conditions that are the subject of the presently pending claims after entry of the above amendment, this reference also fails to provide any indication that serine protease inhibitors will have any activity, much less a therapeutic activity, with respect to the conditions now claimed.

As such, the primary references, i.e., Freidrich, Okajima, Veronesi and Pinsky, all fail to provide any guidance as to the activity of serine protease inhibitors with respect to treatment of disease conditions that are the subject of the presently pending claims following entry of the above amendment.

As Kazmirowski has been cited solely for the teaching of a specific class of compounds as serine protease inhibitors, Kazmirowski fails to make up the fundamental deficiencies in the primary references.

Accordingly, presently pending Claims 26 to 42 are not obvious over the combined teaching of Freidrich, Okajima, Veronesi and Pinsky, in view of Kazmirowski and are therefore patentable over the combined teaching of these references.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number THUR001.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: July 20, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please Cancel Claims 1 to 25.

Please enter the following new claims:

--26. A method of treating a host suffering from a condition characterized by an undesirable increase in synaptic responsiveness, said method comprising:

administering to said host an amount of a serine protease inhibitor effective to treat said host for said condition.

27. The method according to Claim 26, wherein said condition is characterized by the occurrence of sprouting.

28. The method according to Claim 26, wherein said condition is characterized by the occurrence of seizures.

29. The method according to Claim 26, wherein said condition is epilepsy.

30. The method according to Claim 29, wherein said method results in a decrease in seizure proneness.

31. The method according to Claim 26, wherein said host is a mammalian host.

32. A method of treating a host suffering from a condition resulting from excessive activity of glutamate receptors, said method comprising:

administering to said host an amount of a serine protease inhibitor effective to treat said host for said condition.

33. The method according to Claim 32, wherein said excessive activity results from hypoxia, head trauma or stroke.

34. The method according to Claim 32, wherein said host is a mammalian host.

35. A method of treating a host suffering from a condition resulting from exogenous tPA activity, said method comprising:

administering to said host an amount of a serine protease inhibitor effective to treat said host for said condition.

36. The method according to Claim 35, wherein said serine protease inhibitor is administered to said host after administration of exogenous tPA.

37. The method according to Claim 35, wherein said host is a mammalian host.

38. A method of preventing the onset of a condition characterized by increased synaptic responsiveness in a host, which method comprises:

administering to said host an amount of a serine protease inhibitor effective to prevent onset of said condition.

39. The method according to Claim 38, wherein said condition is characterized by the occurrence of sprouting.

40. The method according to Claim 38, wherein said condition is characterized by the occurrence of seizures.

41. The method according to Claim 38, wherein said condition is epilepsy.

42. The method according to Claim 38, wherein said host is a mammalian host. --